REMARKS

Claims 2, 39, 42, 45, 48, 51, 53, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99 and 102 were pending in this application. According to the April 9, 2001 Office Action, claims 51, 54, 57, 60, 63, 66, 69, 72 and 87 were withdrawn and claims 2, 39, 42, 45, 48, 75, 78, 81, 84, 90, 93, 96, 99 and 102 rejected. Applicant has canceled claims 53 and amended claim 2, 84 and 96. Accordingly, claims 2, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99 and 102 are under consideration. Applicant maintains that the amendments do not introduce any new matter.

Claim Withdrawal

The Examiner stated that claim 53 is withdrawn from further consideration as drawn to a non-elected invention. In response, Applicant has hereinabove canceled claim 53 without prejudice.

The Examiner also stated that claims 51, 54, 57, 60, 63, 66, 69, 72 and 87 are withdrawn from further consideration as being drawn to a non-elected species, there being no allowable generic or linking claim. In response, Applicant respectfully traverses the Examiner's withdrawal of these claims. Claim 72 is generic to claim 96 which recites the elected specie. In addition, Claims 51, 54, 57, 60, 63, 66, 69, 72 and 87 are all dependent from elected generic claim 2 which Applicant deems as an allowable claim as discussed hereinbelow. Accordingly, the Examiner is kindly requested to consider these claims during examination.

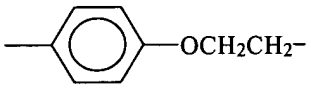
Claim Objections

The Examiner objected to claims 75 and 102 under 37 C.F.R. §1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim.

In response, Applicant respectfully traverses the Examiner's objection to claim 75. Claim 75 further limits the moiety Z which is defined in claim 72 as a bivalent closing moiety to -O-, -NH-, -S- and $-CH_2-$. However, Applicant believes that the Examiner intended to make the objection to claim 78. Nonetheless, Applicant respectfully traverses the Examiner's objection to claim 78 and maintains that claim 78 adds a further limitation to claim 72. Specifically, the

definition of R_{100} in claim 72 is: "a bivalent moiety which distances L from the B-ring by 4-10 intervening atoms."

In claim 78, L G_1G_2 is $N(R_3)R_4$ and R_{100} is represented by:



With regard to the objection to claim 102, Applicant has hereinabove amended claim 2 by adding "and compound converted in vivo to thereof" which was inadvertently omitted. Accordingly, the Examiner is kindly requested to withdraw this objection.

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 2, 39, 42, 45, 48, 75, 78, 81, 84, 90, 93, 96, 99 and 102 under 35 U.S.C. §112, first paragraph, as allegedly based on a disclosure which is not enabling.

In response, Applicant has hereinabove amended claim 2 to indicate that increasing the levels of a sex steroid precursor in a patient is accomplished by administering said sex steroid precursor to said patient. Accordingly, the Examiner is kindly requested to withdraw this rejection.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 2, 39, 42, 45, 48, 75, 78, 81, 84, 90, 93, 96, 99 and 102 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

In response, Applicant has hereinabove amended claim 2 to indicate that increasing the levels of a sex steroid precursor in a patient is accomplished by administering sais sex steroid precursor to said patient.

With regard to the term "modulator," it is a part of a well-defined expression "Selective Estrogen Receptor Modulator" which represents a new class of compounds which are estrogenic in some tissues and antiestrogenic in other. In the specification, this expression is described on page 11, last paragraph and page 12, first paragraph.

"As used herein, a selective estrogen receptor modulator (SERM) is a compound that either directly or through its active metabolite functions as an estrogen receptor antagonist (antiestrogen") in breast tissue, yet provides estrogenic or estrogen-like effect on bone tissue and on serum cholesterol levels (i.e. by reducing serum cholesterol). Non-steroidal compounds that function as estrogen receptor antagonists *in vitro* or in human or rat breast tissue (especially if the compound acts as an antiestrogen on human breast cancer cells) is likely to function as a SERM. Conversely, steroidal antiestrogens tend not to function as SERMs because they tend not to display any beneficial effect on serum cholesterol. Non-steroidal antiestrogens we have tested and found to function as SERMs include EM-800, EM-01538, Raloxifene, Tamoxifen and Droloxifene. We have tested the steroidal antiestrogen ICI 182,780 and found not to function as SERMs."

This term is currently used in literature since 1998. For example: Raymond F. Kauffman et al., "Effects of Estrogen and Raloxifene, a Selective Estrogen Receptor Modulator, in Animal Models of Vascular Injury," Endothelial Cell Res. Ser. (1998), 3(Estrogen and the Vessel Wall), 201-211.

With regard to the term "substantially" in claim 84, Applicant has hereinabove amended claim 84 to delete the term substantially and state that "said compound or salt consists essentially of 2(S)-enantiomer."

With regard to claim 96, Applicant has hereinabove amended this claim to delete the term "an amount of sex steroid precursor...androst-5-ene-3β,17β-diol."

Accordingly, the Examiner is kindly requested to withdraw these rejections.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 2, 39, 42, 45, 48, 75, 78, 81, 84, 90, 93, 96, 99 and 102 under 35 U.S.C. §103(a) as allegedly unpatentable over Ben-David et al., Kelly in view Wojtacki et al., Sharma et al., and Labrie et al.

In response, Applicant respectfully traverses the Examiner's rejection. Applicant throughout the specification has demonstrated the unexpected and synergistic effects of the combination of SERMs and sex steroid precursors on the treatment of the reduction of the risk of

acquiring hypercholesterolemia. For instance, Figure 3 shows that in the rat, DHEA alone has no effect on total cholesterol serum levels, while the addition of DHEA to EM-800 does not prevent the beneficial effect of EM-800 and seems to increase this effect.

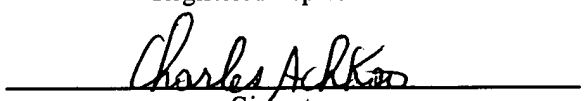
In addition, Applicant also submits herewith a Declaration under Rule 132 showing that a real beneficial effect is obtained by the combination of DHEA and EM-652.HCl on total cholesterol serum levels. A decrease of 73.6% of the total cholesterol concentration (0.65±0.06 mmol/L) is obtained with the combination while this decrease is only of 64.6% (0.87±0.04 mmol/L) or 35.4% (1.59±0.10 mmol/L) with EM-652.HCl or DHEA alone. The addition of DHEA to EM-652.HCl treatment allows for a significant additional reduction of 9% of the cholesterol serum levels.

Accordingly, since Applicant has shown the unexpected and synergistic effects of the claimed combination on breast cancer, the Examiner is kindly requested to withdraw this rejection.

In light of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and the early issuance of a Notice of Allowance is respectfully solicited. If there are any issues or amendments the Examiner wishes to discuss, the Examiner is encouraged to contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on June 28, 2001:

Charles C. Achkar
Name of applicant, assignee or Registered Representative



Signature
June 28, 2001
Date of Signature

WOG/CCA:lac

Respectfully submitted,

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APPENDIX A
"Clean" Version of Each Paragraph/Section/Claim
37 C.F.R. § 1.121(b)(ii) and (c)(i)

CLAIMS (with indication of amended or new):

(Amended) 2. A method of treating or reducing the risk of acquiring hypercholesterolemia comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, androst-5-ene-3β,17β-diol and compound converted in vivo to thereof, in a patient in need of said treatment or said reduction by administering said steroid precursor to said patient, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

(Amended) 84. The method of Claim 81 wherein said compound or salt consists essentially of (2S)-enantiomer.

(Twice Amended) 96. The method of Claim 2 wherein said selective estrogen receptor modulator is:

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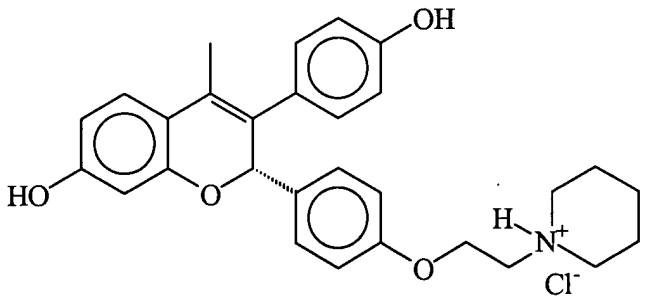
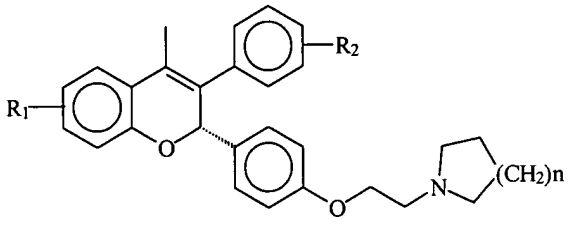


ABSTRACT OF THE DISCLOSURE

Novel methods for the medical treatment and/or inhibition of the development of hypercholesterolemia in susceptible warm-blooded animals including humans involving administration of selective estrogen receptor modulator particularly compounds having the general structure:



and an amount of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androst-5-ene-3β,17β-diol and compounds converted *in vivo* to one of the foregoing precursor. Further administration of bisphosphonates in combination with selective estrogen receptor modulators and/or sex steroid precursor is disclosed for the medical treatment and/or inhibition of the development of osteoporosis. Pharmaceutical compositions for delivery of active ingredient(s) and kit(s) useful to the invention are also disclosed.

APPENDIX B
Version with Markings to Show Changes Made
37 C.F.R. § 1.121(b)(iii) and (c)(ii)

CLAIMS:

2. A method of treating or reducing the risk of acquiring hypercholesterolemia comprising increasing levels of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone-sulfate, [and] androst-5-ene-3β,17β-diol and compound converted in vivo to thereof, in a patient in need of said treatment or said reduction by administering said steroid precursor to said patient, and further comprising administering to said patient a therapeutically effective amount of a selective estrogen receptor modulator as part of a combination therapy.

84. The method of Claim 81 wherein said compound or salt [substantially lacks (2R)-enantiomer] consists essentially of (2S)-enantiomer.

96. The method of Claim 2 wherein said selective estrogen receptor modulator is:

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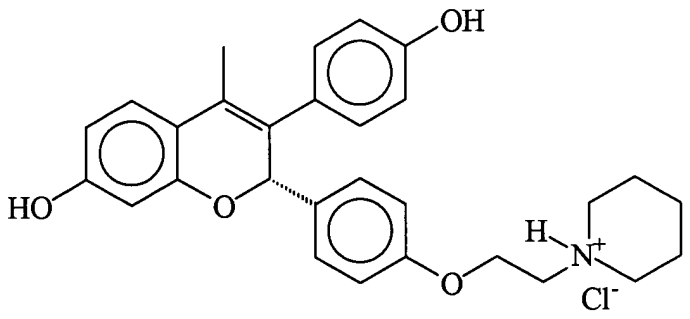
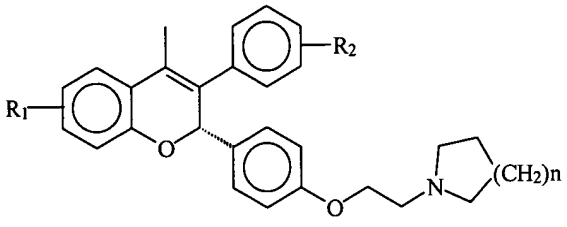


[and an amount of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate and androst-5-ene-3β,17β-diol.]

ABSTRACT OF THE DISCLOSURE

Novel methods for the medical treatment and/or inhibition of the development of [osteoporosis, breast cancer,] hypercholesterolemia[, hyperlipidemia or atherosclerosis] in susceptible warm-blooded animals including humans involving administration of selective estrogen receptor modulator particularly compounds having the general structure:



and an amount of a sex steroid precursor selected from the group consisting of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androst-5-ene-3β,17β-diol and compounds converted *in vivo* to one of the foregoing [presursor] precursor. Further administration of bisphosphonates in combination with selective estrogen receptor modulators and/or sex steroid precursor is disclosed for the medical treatment and/or inhibition of the development of osteoporosis. Pharmaceutical compositions for delivery of active ingredient(s) and kit(s) useful to the invention are also disclosed.